American Public Health Association
Children's Environmental Health Network
Physicians for Social Responsibility

July 16, 2003

Public Information and Records
Integrity Branch (PIRIB) (7502C)
Office of Pesticide Programs (OPP),
Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Re: Characterization of Atrazine Cancer Epidemiology Data. Meeting of the FIFRA Scientific Advisory Panel. July 17, 2003

Attention: Docket ID Number OPP-2003-0186
Federal Register: May 30, 2003 (Volume 68, Number 104, Notices, Page 32488-32490
These comments are submitted by regular mail to the above address, and by email to opp-docket@epa.gov

Dear Sir or Madam:

These comments are being submitted on behalf of public health-related organizations concerned about the human health and environmental risks of the herbicide, atrazine. Atrazine is one of the most commonly used agricultural chemicals in the US, and pollutes waterways throughout the country, including many of those from which communities obtain drinking water. We appreciate the time the members of the Scientific Advisory Panel (SAP) have taken to review this important issue. We appreciate the opportunity to provide comments to the SAP, and hope that they will provide helpful guidance and suggestions as the panel members consider the cancer risk of atrazine.

1. We urge the SAP to recommend using the 2003 Draft Final "Guidelines for Carcinogen Risk Assessment" to evaluate the cancer effects of atrazine. These guidelines were approved by the Scientific Advisory Board at their meeting in May 2003. The SAB also recommended that the Agency finalize the guidelines and begin to use them as rapidly as possible.[i]

2. We urge the SAP to recommend classifying atrazine as a "likely" human carcinogen, based on sufficient evidence of carcinogenicity in animals studies, evidence that atrazine causes events generally known to be associated with tumor formation, and suggestive evidence in humans of an association between atrazine and cancer.

Below is a brief overview of the scientific evidence supporting the conclusion that atrazine is a "likely" human carcinogen, along with the underlying references:

Evidence of carcinogenicity in animal studies

There are data suggesting that atrazine may act to cause cancer in animals by disrupting hormonal cycles, resulting in delayed or disrupted development of reproductive organs. This may extend the window of vulnerability for the affected organs, making them more susceptible to carcinogens. In studies feeding rats atrazine, early onset mammary tumor and pituitary tumors were observed, associated with early or severe estrous cycle disruption. [ii] In more recent work, EPA scientists reported that rats exposed in utero to atrazine had delayed mammary bud outgrowth, and an increase in multiplicity and volume of tumors after exposure to another carcinogen. The authors suggest that by delaying mammary gland development, gestational atrazine exposure increases the susceptibility of female rats to carcinogens, perhaps, by extending the period of vulnerability.[iii]

Evidence that atrazine acts as an endocrine disruptor, and that through this action is likely to cause events associated with tumor formation.

The Scientific Advisory Board (SAB) reviewed the 2003 Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens in June of this year. The SAB recommended that the EPA make their guidance even more protective of early-life stage exposures to endocrine disrupting chemicals. The SAB recognized that "[i]t is likely that early-life stages have windows of susceptibility to carcinogens acting through endocrine disruption".[iv] The SAB stated that there is reason to believe that hormonal agents can be more potent carcinogens when exposure occurs in early-life stages than in later-life stages alone. This raises significant concern, when considering all the data demonstrating endocrine disrupting effects of atrazine. For example, when nursing rats were treated with atrazine the male pups developed prostate gland inflammation.[v] Unfortunately, this experiment was not continued to see if prostatitis would proceed to prostate cancer. Treatment of male and female rats with atrazine from weaning until puberty resulted in delayed sexual maturity.[vi] In two separate laboratories it was reported that testosterone levels were reduced[vii] and sperm motility was reduced, in atrazine-exposed rats.[viii] It was reported in three separate laboratories that frogs living in atrazine-laced water had gonadal deformities, including hermaphroditism.[ix]

Evidence in humans of an association between atrazine and cancer

A recent study of Hispanic farm workers show increased prostate cancer associated with high atrazine exposure. This study reports that Hispanic farm workers with elevated exposure to triazine herbicides (simazine) experienced elevated risk of prostate cancer compared to workers with lower levels of exposure.[x] Risk of prostate cancer was increased approximately 50-80% in the higher use quartiles. The authors report that the relationship was statistically significant in men with more advanced disease at diagnosis (N=94, OR=2.16, 95%CI=1.15-4.04).

Triazine exposures associated with a two or three-fold increase in ovarian cancer in exposed women was reported in a population-based study in Italy.[xi] Although this study population was small (65 women and 126 controls), the findings were statistically significant, and deserve consideration. Notably, these findings support the findings below, from the National Cancer Institute Agriculture Health Study.

The National Cancer Institute Agriculture Health Study reports a significant association between female pesticide applicators in Iowa and North Carolina and ovarian cancer.[xii] While the effect is not directly attributable to any single chemical, large amounts of atrazine are used in the Midwest. 7-8 million pounds of atrazine are applied annually in Iowa, and approximately half-million pounds in North Carolina in 2001.[xiii] These findings will be published in the Scandinavian Journal of Work Environment and Health.

A recently published industry-sponsored study find workers in the atrazine manufacturing plant have elevated prostate and other cancers. EPA and several independent epidemiologists reviewed an occupational study of workers at an atrazine manufacturing plant that found an increase in prostate cancer. EPA concluded that the study is unable to show that atrazine is or is not the cause of the observed cancers. However, we suggest that an elevation of prostate cancer six-fold above background may be significant, and should not be dismissed on the unsupported hypothesis that the cancers are due to increased PSA-screening of employees.

Thank you for your consideration of these comments.

Sincerely,

Don Hoppert
Director of Federal and Congressional Affairs
American Public Health Association

Daniel Swartz
Executive Director
Children's Environmental Health Network

Susan West Marmagas, MPH
Director, Environment and Health Program
Physicians for Social Responsibility

[i] Draft report of the SAB. Supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogenesis (SCACS) review panel. June 20, 2003. Available electronically at http://www.epa.gov/sab/pdf/sgacsdftrpt062003.pdf

ii Eldridge JC, Tennant MK, Wetzel LT, Breckenridge CB, Stevens JT. Factors affecting mammary tumor incidence in chlorotriazine-treated female rats: hormonal properties, dosage, and animal strain. Environ Health Perspect. 1994 Dec;102 Suppl 11:29-36.

Wetzel LT, Luempert LG 3rd, Breckenridge CB, Tisdel MO, Stevens JT, Thakur AK, Extrom PJ, Eldridge JC. Chronic effects of atrazine on estrus and mammary tumor formation in female Sprague-Dawley and Fischer 344 rats. J Toxicol Environ Health. 1994 Oct;43(2):169-82.

Eldridge JC, Wetzel LT, Tyrey L. Estrous cycle patterns of Sprague-Dawley rats during acute and chronic atrazine administration. Reprod Toxicol. 1999 Nov-Dec;13(6):491-9.

Eldridge JC, Wetzel LT, Stevens JT, Simpkins JW. The mammary tumor response in triazine-treated female rats: a threshold-mediated interaction with strain and species-specific reproductive senescence. Steroids. 1999 Sep;64(9):672-8. Review.

[iii] Fenton SE, Davis CC. 2002. Atrazine exposure in utero increases dimethylbenz[a]anthracene-induced mammary tumor incidence in long evans offspring. Society of Toxicology Abstr., p. 185

iv Draft report of the SAB. Supplemental guidance for assessing cancer susceptibility from early-life exposure to carcinogenesis (SCACS) review panel. June 20, 2003. Available electronically at http://www.epa.gov/sab/pdf/sgacsdftrpt062003.pdf

v Stoker TE, Robinette CL, Cooper RL. Maternal exposure to atrazine during lactation suppresses suckling-induced prolactin release and results in prostatitis in the adult offspring. Toxicol Sci. 1999;52(1):68-79.

vi Stoker TE, Laws SC, Guidici DL, Cooper RL. The effect of atrazine on puberty in male wistar rats: an evaluation in the protocol for the assessment of pubertal development and thyroid function. Toxicol Sci. 2000 Nov;58(1):50-9.

[vii] Friedmann AS. Atrazine inhibition of testosterone production in rat males following peripubertal exposure. Reprod Toxicol. 2002 May-Jun;16(3):275-9.

viii Kniewald J, Jakominic M, Tomljenovic A, et al. Disorders of male rat reproductive tract under the influence of atrazine. J Appl Toxicol. 2000;20(1):61-8

ix Tavera-Mendoza L, Ruby S, Brousseau P, Fournier M, Cyr D, Marcogliese D. Response of the amphibian tadpole Xenopus laevis to atrazine during sexual differentiation of the ovary. Environ Toxicol Chem. 2002;21(6):1264-7.

ix Carr JA, Gentles A, Smith EE, Goleman WL, Urquidi LJ, Thuett K, Kendall RJ, Giesy JP, Gross, TS, Solomon, KR, Van Der Kraak, G. Response of larval Xenopus laevis to atrazine: Assessment of growth, metamorphosis, and gonadal and laryngeal morphology. Environ Toxicol Chem. 22: 396-405 (2003).

ix Hayes T, Haston K, Tsui M, Hoang A, Haeffele C, Vonk A. Atrazine-Induced Hermaphroditism at 0.1 ppb in American Leopard Frogs (Rana pipiens): Laboratory and Field Evidence. Environ Health Perspect. 2003 Apr;111(4):568-75.

[x] Mills PK, Yang R. Prostate cancer risk in California farm workers. J Occup Environ Med. 2003 Mar;45(3):249-58.

[xi] Donna A, Crosignani P, Robutti F, Betta PG, Bocca R, Mariani N, Ferrario F, Fissi R, Berrino F. Triazine herbicides and ovarian epithelial neoplasms. Scand J Work Environ Health. 1989 Feb;15(1):47-53.

[xii] Alavanja M et al. 2003. National Cancer Institute Agriculture Health Study. Unpublished.

[xiii] National Agriculture Statistics Service (NASS).Agricultural chemical use database. http://www.pestmanagement.info/nass/app_usage.cfm